Pregnancy Characteristics and Maternal Risk of Breast Cancer

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In a population-based case-control study of parous women less than 45 years of age, we evaluated the relations of various pregnancy characteristics to maternal breast cancer risk. Cases (N = 1,239) diagnosed with *in situ* or invasive breast cancer from 1990 to 1992 in Atlanta, GA, Seattle/Puget Sound, WA, and five counties in central New Jersey, and population controls (N = 1,166) identified by random-digit dialing, were interviewed regarding the details of their pregnancies. We used logistic regression to estimate relative risks (RR) and 95% confidence intervals (CI) and to adjust for breast cancer risk factors. Women who reported nausea or vomiting in their first pregnancy had a slightly lower risk of breast cancer (RR = 0.87; 95% CI = 0.72–1.0). We found no strong or consistent associations for maternal risk related to gestational length, pregnancy weight gain, gestational diabetes, pregnancy hypertension, or gender of the offspring, although we found some evidence for reductions in risk for toxemia (RR = 0.81; 95% CI = 0.61–1.1) and specific sex (RR for female twins *vs* singletons = 0.48; 95% CI = 0.20–1.3) and timing characteristics of twinning. Overall, these data provide little support for the hypothesis that pregnancy hormone levels are associated with subsequent maternal risk of breast cancer in young women. (Epidemiology 1998;9:641–647)

Keywords: breast cancer, pregnancy, twinning, toxemia, weight gain, gestational diabetes.

Nulliparity is a risk factor for breast cancer, and studies among parous women have shown that each pregnancy confers a small additional reduction in risk.[1] A first full-term pregnancy before the age of 30 years, in addition, is one of the strongest identified factors protective against the development of breast cancer.[1] The biological mechanisms underlying the association between pregnancy and breast cancer risk are unclear. One of the major hypotheses involves permanent changes in breast tissue susceptibility brought about by cellular differentiation of the mammary gland.[2] Animal studies suggest that the placental hormone human chorionic gonadotropin (hCG) may be involved in this process.[3] In addition, epidemiologic data show a reduced risk of breast cancer among parous and nulliparous women treated with hCG.[4] Alpha-fetoprotein (AFP), shown to regress estrogen-dependent breast tumors in rats, has also been hypothesized to mediate the protective effect of pregnancy.[5]

Physiologic conditions associated with altered pregnancy hormone levels may be useful in evaluating the role of pregnancy hormones in the development of breast cancer. Twin pregnancies are associated with a variety of unusual hormone profiles, including hCG levels more than twice those of singleton pregnancies.[6] Maternal hCG levels in pregnancies with a female fetus also are substantially higher than in those with a male fetus.[7] Although the cause of pregnancy nausea is uncertain, some studies show associations with higher levels of estrogen[8] and hCG,[9,10] whereas other studies do not.[8,9,11] In addition, serum maternal AFP levels are elevated in twin pregnancies[12] and in pregnancies with hypertension.[13]

A large population-based case-control study collected detailed information on self-reported pregnancy characteristics, providing the opportunity to assess whether breast cancer risk is modified by various aspects of full-term pregnancies.

Subjects and Methods

This population-based case-control study was conducted in three geographic areas in the United States covered by cancer registries: Atlanta, GA; Seattle/Puget Sound, WA; and five counties in central New Jersey. Details are

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published elsewhere.[14] Briefly, the present analysis comprises all women 20–44 years of age in Seattle, New Jersey, and Atlanta who were newly diagnosed with *in situ* or invasive breast cancer during the period May 1, 1990, through December 31, 1992. Cases were identified through rapid ascertainment systems, and hospital records of eligible patients were abstracted to document details on the clinical and pathologic characteristics of the diagnosed breast cancers. Controls were chosen through random-digit dialing and were frequency matched by age and geographic area to the expected distribution of cases.[15] A 90.5% response rate to the telephone screener was obtained from 16,254 residential telephone numbers.

Structured in-person interviews were obtained from 1,669 of the 1,940 eligible cases (86.0%), and 1,505 of the 1,912 eligible controls (78.7%). The primary reason for incomplete interviews was refusal (5.8% physician refusal and 6.7% case and 12.9% control subject refusal). Among the controls, the overall response rate was 71.2% (telephone screener rate times the interview response rate). The interview lasted an average of 67 minutes and included detailed information about demographic factors, reproductive and menstrual history, contraceptive behavior, breastfeeding, use of exogenous hormones, screening history, smoking, and alcohol consumption. All information on risk factors was truncated at the date of diagnosis for cases and the date of completion of the telephone screener for controls (except alcohol consumption, which was truncated at 2 years before diagnosis or screener). To make the cases comparable with the controls, we excluded from the analyses 29 cases without residential telephones. We also excluded 19 controls previously diagnosed with breast cancer. Of the remaining 1,640 cases and 1,486 controls, 1,239 (75.0%) and 1,166 (79.0%), respectively, were parous (had a livebirth or stillbirth) and formed the study population for the present analyses. Fourteen women (0.6%) (7 cases and 7 controls) had a stillbirth only.

The subjects were queried regarding the details of their pregnancies. Length of gestation was obtained for all pregnancies, but information on all other pregnancy characteristics was obtained only for pregnancies resulting in a livebirth or stillbirth. Women were asked, for each pregnancy, how many pounds they had gained; whether they had frequent nausea or vomiting, and in which months; and whether they had ever developed hypertension or high blood pressure, toxemia, diabetes, high blood sugar, or any other pregnancy-related complications. We defined women as postmenopausal if they had undergone either a natural menopause (no menses for at least 6 months before interview date) or surgery to remove both ovaries. We considered women who had undergone surgery not involving removal of both ovaries premenopausal, because the analyses were restricted to women who were less than 45 years of age, younger than the median age at natural menopause in the United States.

We evaluated relative risks (RR) and 95% confidence intervals (CI) from multiple logistic regression.[16] We adjusted effect estimates for site and age at diagnosis or telephone screener. The effect estimates were further adjusted for breast cancer risk factors found to be associated with the pregnancy characteristics evaluated, in addition to race and study site. The RR estimates for pregnancy characteristics were similar when adjusted for all of the demonstrated breast cancer risk factors.

Results

The risk factors for breast cancer among this subset of parous women were generally similar to those demonstrated for the entire study population (Table 1). We evaluated length of gestation for all reported pregnancies, adjusting for age and study site. Risk was not associated with length of the first pregnancy, the shortest pregnancy, the average length of all pregnancies, or the total length of all pregnancies combined [for all four variables treated as continuous, the RR for each week of pregnancy was 1.0 (95% CI = 0.99–1.0)]. In addition, there was little association with risk when gestational length was considered as categorical (categories were: <13, 13–23, 24–27, 28–31, 32–37, 38–39, and ≥40 weeks). The results for pregnancy length were similar when restricted to livebirths or stillbirths. There was little association of risk with weight gain in the first pregnancy or maximum weight gain (Table 2), and the results were essentially unchanged with adjustment for potential confounding factors. Further analyses showed little association with minimum pregnancy weight gain, or average weight gained in all pregnancies resulting in a livebirth or stillbirth (results not shown). Results for pregnancy weight gain were similar when stratified by levels of prepregnancy or current weight (results not shown).

Toxemia and hypertension during pregnancy were associated with modest reductions in the risk of breast cancer (Table 3). Adjustment for potential confounders attenuated these associations, although only slightly for toxemia (RR = 0.81; 95% CI = 0.61–1.1). Approximately 38% of women who reported having hypertension also reported having toxemia during at least one pregnancy. When we excluded these women, the results for hypertension were unchanged (results not shown). Women who reported nausea or vomiting during at least one of their pregnancies had a reduced RR that was attenuated slightly with adjustment for covariates (RR = 0.91; 95% CI = 0.77–1.1). The RR for nausea or vomiting was only slightly lower when these conditions occurred in the first pregnancy (RR = 0.87; 95% CI = 0.72–1.0). Similarly, none of the other effect estimates in Table 3 varied substantially by whether the condition occurred in the first pregnancy or subsequent pregnancies. The effect estimates observed for toxemia and nausea or vomiting were unchanged with simultaneous adjustment for each other (results not shown).

In Table 3, we present effect estimates for the pregnancy conditions by strata of years since last pregnancy

TABLE 1. Distribution of Risk Factors and Associated Relative Risks (RR) for Breast Cancer among Parous Cases and Control Subjects Younger than 45 Years of Age

Risk Factor	Cases	Controls	RR*	95% CI
Race				
White†	958	903	1.0	
African-American	213	183	1.3	0.97–1.6
Other	68	80	0.88	0.62–1.3
Education				
≤ High school†	355	358	1.0	
Technical school	94	104	0.85	0.61–1.2
Some college	334	323	0.95	0.76–1.2
College graduate	287	241	1.1	0.82–1.4
Postgraduate work	169	140	1.0	0.74–1.4
Number of births				
≥4†	84	126	1.0	
3	221	240	1.4	1.0–2.1
2	598	503	1.8	1.3–2.4
1	336	297	1.7	1.2–2.4
Age (years) at first birth				
<20†	220	256	1.0	
20–24	372	370	1.1	0.87–1.4
25–29	361	324	1.2	0.94–1.6
≥30	285	216	1.4	1.0–1.8
Years since last pregnancy ended				
<5†	339	316	1.0	
5–9	333	294	1.0	0.80–1.3
≥10	550	507	0.94	0.72–1.2
Months breastfed				
0†	508	443	1.0	
<12	446	421	0.93	0.76–1.1
12–23	159	167	0.82	0.62–1.1
≥24	119	128	0.90	0.65–1.2
Number of spontaneous abortions				
0†	924	885	1.0	
1	230	199	1.1	0.92–1.4
≥2	65	57	1.1	0.77–1.6
Number of induced abortions				
0†	966	902	1.0	
1	196	188	0.94	0.75–1.2
≥2	60	55	0.97	0.66–1.4
Years of oral contraceptive use				
0†	273	317	1.0	
<5	528	466	1.3	1.0–1.6
5–10	286	256	1.2	0.98–1.6
≥10	152	127	1.3	0.93–1.7
Age (years) at menarche				
≥14†	225	246	1.0	
13	330	348	1.0	0.82–1.3
12	368	309	1.3	1.0–1.7
<12	314	263	1.3	1.0–1.7
Menopausal status				
Premenopausal†	1215	1115	1.0	
Postmenopausal	23	48	0.47	0.28–0.79
Mother or sister with breast cancer				
No†	1074	1085	1.0	
Yes	164	81	2.0	1.5–2.7
Previous breast biopsy				
No†	1127	1090	1.0	
Yes	112	76	1.4	0.99–1.8
Body mass index‡				
<22†	333	276	1.0	
22–24.59	290	293	0.83	0.66–1.0
24.6–29.02	302	290	0.90	0.71–1.1
≥29.03	287	288	0.82	0.64–1.0
Alcohol intake§ (drinks)				
Never-drinker†	468	481	1.0	
Past drinker	57	47	1.3	0.86–2.0
1/week to <2/day	654	600	1.1	0.93–1.3
≥2/day	59	36	1.7	1.1–2.7

* Standard logistic model included study site, age (as a continuous variable), race, number of births, and age at first birth. All other variables were entered individually to the standard model. Unknowns were included in the analyses but are not presented in the table.
† Referent category.
‡ Body mass index calculated as weight (kg) divided by height (m^2).
§ Alcohol intake within the 5-year period up to the reference date.

to evaluate whether the short- and long-term effects of pregnancy conditions on risk differed. The RR for gestational diabetes was below 1.0 among women whose last pregnancy ended within the last 5 years, whereas it was greater than 1.0 for women whose last pregnancy ended 5 or more years in the past. The RR for toxemia was close to 1.0 among women with a recent pregnancy but lower than 1.0 for women whose last pregnancy was in the more distant past. The effect estimates for pregnancy hypertension and nausea and vomiting differed little by time since last pregnancy.

Because of the large number of women reporting nausea or vomiting during the first pregnancy, we were able to explore this association further (Table 4). Breast cancer risk was similar for nausea with and without vomiting. Risk was lowest when nausea or vomiting occurred in both the first and second trimesters, but we saw no further reduction when it continued into the third trimester. Separate analyses evaluating number of pregnancies with nausea or vomiting were stratified by parity to avoid confounding. Among women with two livebirths or stillbirths, risk was lower among those who reported experiencing nausea or vomiting in both pregnancies (adjusted RR = 0.79; 95% CI = 0.58–1.1) than among those who reported it in the first pregnancy only (adjusted RR = 0.89; 95% CI = 0.62–1.3), although number of pregnancies with nausea or vomiting (treated as a categorical variable) showed little association with risk among women with three or four pregnancies resulting in livebirths or stillbirths (results not shown).

Breast cancer risk did not differ greatly by whether subjects had ever had twins compared with having had singletons only (Table 5). There was some variation in the effect estimates for twinning, however, when evaluated by birth order, age at first twin birth, time since first twin birth, and sex of the twins. Although there was little difference in risk among women who had twins as a first birth compared with women who had a singleton, risk was slightly reduced for twins occurring as a last birth. Risk appeared reduced also for twin births that oc-

TABLE 2. Relative Risks (RR) of Maternal Breast Cancer by Pregnancy Weight Gain

Risk Factor*	Cases	Controls	RR†	95% CI	RR‡	95% CI
Weight gain (lb) in first pregnancy§						
≤22.5	289	261	0.99	0.75–1.3	1.0	0.78–1.4
22.6–27.5‖	165	150	1.0		1.0	
27.6–32.5	167	161	0.95	0.70–1.3	0.93	0.68–1.3
32.6–37.5	89	73	1.2	0.79–1.7	1.1	0.74–1.6
37.6–42.5	86	105	0.76	0.53–1.1	0.75	0.52–1.1
>42.5	158	139	1.1	0.79–1.5	1.1	0.79–1.5
Maximum weight gain (lb)¶						
≤22.5	232	197	1.0	0.78–1.4	1.1	0.80–1.4
22.6–27.5‖	192	169	1.0		1.0	
27.6–32.5	206	200	0.92	0.69–1.2	0.88	0.66–1.2
32.6–37.5	126	127	0.90	0.65–1.2	0.88	0.63–1.2
37.6–42.5	170	174	0.88	0.65–1.2	0.88	0.65–1.2
42.6–47.5	69	57	1.1	0.74–1.7	1.1	0.72–1.7
47.6–52.5	97	97	0.90	0.64–1.3	0.91	0.63–1.3
>52.5	129	128	0.94	0.68–1.3	0.94	0.68–1.3

* For women with only one pregnancy, the weight gain variables have the same value. Numbers of cases and controls do not add to 1,239 and 1,166 owing to missing values on pregnancy weight gain.
† Adjusted for age and site.
‡ Basic model includes age, site, race, and a combination variable representing parity and age at first birth. Weight gain in first pregnancy is also adjusted for current body mass index (BMI), age at menarche, recent alcohol intake, and years of oral contraceptive (OC) use; maximum weight gain is also adjusted for BMI, age at menarche, mammography, alcohol intake, and OC use. Results were similar when BMI was not included in the models.
§ Excludes 267 cases and 260 controls whose first pregnancy did not result in a livebirth or stillbirth.
‖ Referent category.
¶ Maximum weight gain represents weight gain in all pregnancies resulting in a livebirth or stillbirth.

curred at 25 years of age or older and for those that occurred within 15 years of diagnosis. Assessing twin pregnancies by sex was done in an attempt to separate monozygotic from dizygotic pregnancies, because in the latter there are two placentas. Opposite-sex twins are dizygotic, whereas same sex-twins may be either dizygotic or monozygotic. Compared with mothers of singletons only, mothers of female twins were at lower risk of breast cancer, whereas risk appeared to be increased for mothers of male twins, although these results were based on small numbers.

Among women with singleton births only, breast cancer risk did not vary substantially by whether the first liveborn or stillborn child was male or female (age-adjusted RR for female *vs* male = 0.94; 95% CI = 0.78–1.1). Analyses evaluating numbers of sons and daughters (stratified by parity to avoid confounding) also showed little association with risk (results not shown).

Discussion

In this large study of young (20–44 years of age), parous women, nausea or vomiting during pregnancy was associated with a small reduction in breast cancer risk. In addition, women who ever reported having pregnancy toxemia had a small deficit in breast cancer risk. Our findings also indicated a reduction in risk among women who carried two female twins compared with women who had singleton pregnancies. We noted no important difference in risk by gestational length, pregnancy weight gain, gestational diabetes, pregnancy hypertension, or sex of offspring.

Our findings with regard to pregnancy toxemia (a term that includes both preeclampsia and eclampsia and consists of hypertension, proteinuria, and edema) were in the same direction but less pronounced than those of two previous case-control studies.[5,17] The lack of an overall association between twinning and maternal breast cancer risk in the present study confirms the findings of other researchers,[17–20] although two studies have shown a lower risk among mothers of multiple births compared with mothers of singletons,[21,22] and in one study,[21] as in ours, risk was slightly lower for twins occurring in the last pregnancy. Maternal breast cancer risk was elevated in another study of twinning.[23] The details of twinning, however, could not be evaluated well in our study because of the small numbers of exposed subjects. Our finding of little association with sex of the first offspring of a singleton pregnancy agrees with those of the only other study to assess this relation.[24]

Our finding of a slight reduction in maternal breast cancer risk associated with nausea or vomiting during pregnancy is in disagreement with the recent findings by Enger *et al.*[25] There are several differences between the studies that may explain the inconsistent results. Enger *et al* included only women who were treated for nausea, and thus their results might reflect the effects of treatment or severity of nausea. We were unable to evaluate the effects of treatment, because we did not have this information. Another possible explanation for the difference in findings is that information on nausea was ascertained only for completed pregnancies, whereas Enger *et al*[25] obtained this information for all pregnancies. The effects of nausea in completed and uncompleted pregnancies may be different. Finally, the deficit in breast cancer risk that we observed among women who experienced nausea and vomiting was small and may have been due to chance.

An increase in breast cancer risk immediately after pregnancy has been noted in some studies[26] and is hypothesized to be due to the relatively high levels of pregnancy estrogens. It is possible that if nausea reflects elevated hormone levels, risk would be increased immediately after pregnancy but, as is observed with pregnancy itself, would decrease over time and finally become less than that among women who did not experience pregnancy nausea. Our data, however, provide little evidence for this hypothesis, because the small reduction in risk noted for nausea or vomiting was only slightly more pronounced among women whose last pregnancy occurred 5 or more years in the past. The findings by Enger *et al*[25] are more consistent with this possibility, because the increase in breast cancer risk

TABLE 3. Relative Risks (RR) of Maternal Breast Cancer by History of Pregnancy Complications

Risk Factor	Cases	Controls	RR*	95% CI	RR†	95% CI
Gestational diabetes						
Never‡	1,168	1,098	1.0		1.0	
Ever	67	65	0.99	0.70–1.4	1.1	0.73–1.5
First pregnancy	21	18	1.1	0.59–2.1	1.1	0.57–2.1
Last pregnancy <5 years ago						
Never‡	313	287	1.0		1.0	
Ever	25	28	0.83	0.47–1.5	0.88	0.48–1.6
Last pregnancy ≥5 years ago						
Never‡	840	767	1.0		1.0	
Ever	40	32	1.2	0.74–1.9	1.3	0.77–2.1
Toxemia						
Never‡	1,139	1,041	1.0		1.0	
Ever	97	121	0.75	0.57–1.0	0.81	0.61–1.1
First pregnancy	54	66	0.77	0.53–1.1	0.81	0.56–1.2
Last pregnancy <5 years ago						
Never‡	311	285	1.0		1.0	
Ever	27	30	0.88	0.51–1.5	0.97	0.55–1.7
Last pregnancy ≥5 years ago						
Never‡	811	709	1.0		1.0	
Ever	70	89	0.71	0.51–0.98	0.76	0.54–1.1
Hypertension						
Never‡	1,086	1,003	1.0		1.0	
Ever	150	160	0.89	0.70–1.1	0.94	0.73–1.2
First pregnancy	81	75	1.0	0.74–1.4	1.0	0.73–1.4
Last pregnancy <5 years ago						
Never‡	286	261	1.0		1.0	
Ever	52	54	0.92	0.60–1.4	0.92	0.60–1.4
Last pregnancy ≥5 years ago						
Never‡	786	699	1.0		1.0	
Ever	95	100	0.87	0.64–1.2	0.95	0.69–1.3
Nausea/vomiting						
Never‡	554	477	1.0		1.0	
Ever	681	686	0.86	0.73–1.0	0.91	0.77–1.1
First pregnancy	445	463	0.82	0.68–0.98	0.87	0.72–1.0
Last pregnancy <5 years ago						
Never‡	158	140	1.0		1.0	
Ever	180	175	0.92	0.67–1.3	0.94	0.68–1.3
Last pregnancy ≥5 years ago						
Never‡	388	315	1.0		1.0	
Ever	492	484	0.83	0.68–1.0	0.89	0.73–1.1

* Adjusted for age and site. Numbers of cases and controls do not add to 1,239 and 1,166 owing to missing values on pregnancy characteristics.
† Basic model includes age, site, race, and a combination variable representing parity and age at first birth. Gestational diabetes is also adjusted for body mass index (BMI), age at menarche, mammography, and alcohol intake; toxemia is also adjusted for BMI and menopausal status; hypertension is also adjusted for BMI and menopausal status; and nausea/vomiting is also adjusted for years of oral contraceptive use.
‡ Referent category.

with nausea noted in their study was limited to pregnancies occurring within the past 5 years.

If hCG promotes mammary gland differentiation during pregnancy, as suggested by Russo *et al*,[2] then higher levels of hCG might protect against risk in a dose-dependent manner. To the extent that the pregnancy conditions studied are representative of altered hCG levels, some of our observations provide limited evidence in support of this hypothesis. Pregnancy nausea and vomiting, which has been associated in some studies with higher maternal levels of hCG,[9,10] was associated with a lower breast cancer risk. Furthermore, these data indicate that risk associated with female twin sets was reduced compared with singleton births. hCG levels in twin pregnancies involving at least one female have been shown to be higher than those in twin pregnancies involving males only or in male or female singleton pregnancies.[27] Other evidence, however, does not support a role for hCG. Risk associated with female-male twin sets, as well as twinning in general compared with singletons, and female singletons compared with male singletons, was not reduced. In addition, studies of hCG and nausea have not been consistent,[8–10] and some have been criticized for design issues and assays used. Our data were less supportive of a protective effect of AFP. Although toxemia, which has been associated with relatively high levels of AFP,[12] was associated with a slight decrease in breast cancer risk in our study, twinning, which is also associated with relatively high AFP levels,[13] overall was not.

There were several limitations of our study. First, the information was self-reported and recalled from several years earlier with no validation by medical records. Any random misclassification in these data would bias our results toward the null and could explain the largely negative results we observed. Systematic recall bias, whereby cases or controls reported the details of their pregnancies more accurately, could explain the results we observed for toxemia and for nausea or vomiting, although it is unclear why controls would report these conditions more frequently than cases. Also, the response to the interview was lower for controls than cases. The number of cases was limited for some of the exposures and was especially problematic in the analyses evaluating characteristics of twin pregnancies. In addition, information on treatment of the pregnancy complications was not collected. Furthermore, data for all of the pregnancy characteristics except gestational length were available only for pregnancies resulting in a livebirth or stillbirth, limiting the generalizability of our results. For example, these data could not address risk associated with severe complications that result in pregnancy loss.

Overall, these data on parous women provide evidence of a weak protective effect of nausea or vomiting. No strong evidence was found for effects of other preg-

TABLE 4. Relative Risks (RR) of Maternal Breast Cancer by Details of Nausea and Vomiting in the First Pregnancy

Risk Factor	Cases	Controls	RR*	95% CI
Nausea/vomiting†				
Never for both‡	554	477	1.0	
Nausea only	165	164	0.86	0.66–1.1
Nausea and vomiting	274	294	0.88	0.71–1.1
Nausea or vomiting (trimesters)§				
First only	272	250	0.98	0.79–1.2
First and second only	68	98	0.65	0.46–0.91
First, second, and third	89	99	0.81	0.59–1.1

* Model includes age, site, race, a combination variable representing parity and age at first birth, and years of oral contraceptive use.
† Six cases and five controls who reported vomiting without nausea were not included in the analysis.
‡ Referent category.
§ Sixteen cases and 16 controls who reported patterns for nausea or vomiting not noted in the table (for example, second trimester only) were not included in the analyses.

TABLE 5. Relative Risks (RR) of Maternal Breast Cancer Associated with Having a Twin Birth

Risk Factor	Cases	Controls	RR*	95% CI	RR†	95% CI
Singleton (all births)‡	1,198	1,125	1.0		1.0	
Twin birth (at least one)	35	37	0.90	0.56–1.4	0.94	0.58–1.5
Birth order						
Twins in first birth	15	16	0.95	0.46–1.9	0.95	0.47–2.0
Twins in later birth	20	21	0.87	0.47–1.6	0.93	0.50–1.7
Twins in last birth	20	24	0.80	0.44–1.5	0.80	0.44–1.5
Twins in earlier birth	15	13	1.1	0.51–2.3	1.2	0.56–2.6
Age (years) at first twin birth						
≤25	16	15	1.0	0.50–2.1	1.1	0.54–2.3
>25	18	22	0.78	0.42–1.5	0.78	0.41–1.6
Time (years) since first twin birth						
<15 years	17	26	0.66	0.35–1.2	0.65	0.35–1.2
≥15 years	16	11	1.3	0.59–2.8	1.4	0.65–3.1
Sex of twins						
Female/female	7	14	0.48	0.19–1.2	0.51	0.20–1.3
Male/male	14	9	1.5	0.64–3.4	1.5	0.63–3.4
Male/female	14	14	0.96	0.45–2.0	0.98	0.46–2.1

* Adjusted for age and site. Numbers of cases and controls do not add to 1,239 and 1,166 owing to missing values on characteristics of twinning.
† RR further adjusted for site, race, a combination variable representing parity, and age at first birth. Risk estimates were similar when adjusted for history of fertility problems and fertility drug use.
‡ Referent category.

nancy characteristics, including gestational length, weight gain, gestational diabetes, pregnancy hypertension, or sex of the first offspring, although protective effects were suggested for toxemia and certain specific aspects of twinning. Taken together, these findings provide little support for the role of hCG in the reduction of breast cancer risk associated with pregnancy.

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